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RESEARCH ARTICLE

IRON DEFICIENCY ANEMIA AS RISK FACTOR FOR THINNING OF PERIPAPILLARY RETINAL NERVE FIBER LAYER THICKNESS.

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Abstract

Purpose:- To compare thickness of peripapillary retinal nerve fiber layer (RNFL) in adult females having iron deficiency anemia (IDA) with age matched healthy control females by using spectral domain optical coherence tomography (OCT).

Materials and Methods:- The study was conducted upon 30 adult female patients who had IDA (hemoglobin <12 g/dl, serum iron <50 µg/dl mean corpuscular volume <80 fl/ red cell) and 30 age matched healthy control females .complete ophthalmic examination (assessment of refraction and best corrected visual acuity ,intraocular pressure (IOP) measurement by Goldmannapplanation tonometry and fundus examination with C/D ratio assessment).Measurement of peripapillary retinal nerve fiber layer thickness by spectral domain optical coherence tomography . Blood analysis for hemoglobin, serum iron and mean corpuscular volume.

Results:- Mean age of 30 adult anemic female patients was 33.57 ± 7.48 (range, 20–47) years, and of 30 healthy control females was 33.77 ± 6.32 (range, 22–46) years (P = 0.87). The mean RNFL thickness in anemic female patients was 89.5 ± 2.014, and in healthy control females was 94.22 ± 1.486 (P = 0.000026). The mean of inferior quadrant RNFL thicknesses of anemic female patients was 118.83 ± 2.75, and in healthy control females was 124.47 ± 1.93 (P = 0.000032). The mean of superior quadrant RNFL thicknesses of anemic female patients was 109.83 ± 2.3, and in healthy control females was 114.47 ± 1.7 (P = 0.00043). The mean of nasal quadrant RNFL thicknesses of anemic female patients was 69.4 ± 1.81, and in healthy control females was 73.7 ± 1.7 (P = 0.000028). The mean of temporal quadrant RNFL thicknesses of anemic female patients was 59.93 ± 1.95, and in healthy control females was 64.3 ± 1.7 (P = 0.00053). There was positive correlation between mean RNFL thickness and hemoglobin ($r1$ = 0.537, p1=0.002) and iron (r 2= 0.328, p2=0.005).

Conclusions:- There is statically significant reduction of the thickness of peripapillary RNFL thickness measured by OCT in adult female patients with IDA compared to healthy control females. It may have a great impact on assessment of many diseases as glaucoma and neuro-ophthalmological disorder.

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Introduction:-

The most common type of anemia is iron deficiency anemia, especially in women of child bearing age .It occurs when body stores of iron drop too low to supportnormal red blood cell, which store and carry oxygen in blood.[1] Iron deficiency anemia affect ocular structures through ischemia [2] and decrease of iron store.[3]

As regards to iron, it is essential for normal myelination. Oligodendrocytes which normally contain high concentrations of iron-containing enzymes [3] , are responsible for normal myelination. Iron deficiency affects the function of oligodendrocytes and may inhibit the myelination process.[4] In addition to reduction of visual evoked potential. Also reduction of iron may lead to dopaminergic dysfunction which affects area of axons and ganglion cells, which form retinal nerve fiber layer (RNFL). [5],[6]

As regards to ischemia, Inner retinal layers are more susceptible to hypoxia. Retinal ganglion cells are damaged when blood perfusion and oxygen saturation decrease. In addition to hypoxia leads to neuronal death. [7],[8]

It is well known that ,retinal ischemia plays a significant role in development and progression of many ocular disorder as diabetic retinopathy ,glaucoma ,vascular occlusion, retinopathy of prematurity and sickle cell anemia.[2]

Optical coherence tomography is a noninvasive technique for high-resolution, cross-sectional topographic imaging of tissue by measuring backscattered light. The device works on the principal of low coherence interferometry. Images are made by emission of low coherence near infrared light (850nm) from a superluminescent diode laser source and subsequent backscattering from retina. RNFL thickness is measured by the number of pixels between the anterior and posterior reflection from the RNFL identified by an edge detection algorithm. [9][10]

The 3 dimensional OCT (3D-OCT) uses fourier domain instead of time domain, this gives more data in less time by increasing the number of axial scans per second up to 40000. It is 50-100 times faster that allows of reconstructing 3-dimentional images with point to point registration of scanned area. [11]

Quantitative RNFL thickness measurement is a key in diagnosis and monitoring of many ocular diseases as glaucoma ,optic neuropathies, ischemic retinal disorders and multiple sclerosis. [12] [13] Spectral domain optical coherence tomography (SD-OCT) has advantage of enhancement of image resolution, improvement of measurement, reducing the scan time and reproducibility. [14]

In the current study, we aimed to evaluate the effect of iron deficiency anemia (IDA) on peripapillary RNFL thickness in adult female patients with SD- OCT.

Patient and Method:-

The study was carried out from May 2015 to May 2016 on 30 adult female patients who had IDA (hemoglobin <12 g/dl, serum iron <50 µg/dl, mean corpuscular volume <80 Fl/red cell) and 30 age matched healthy control females. The patients were selected from outpatient ophthalmology clinic of Benha University hospital. Informed consent was written from all patients.

The inclusion criteria for all subject were the best corrected visual acuity of 20/20,spherical refraction between -3.0 and +3.0 diopters(D),normal IOP (<20mmHg) ,and normal cup-to-disc ratio(C/D <0.4).

The exclusion criteria were: history of trauma or intraocular surgery, refractive error more than 3D, ocular hypertension or glaucoma (IOP>21mmHg), diabetic retinopathy, cataract or media opacity, uveitis or any vitreoretinal disorder.

Each subject underwent Complete a ophthmalogic examination including: refraction the best corrected visual acuity measurement, slit lamp biomicroscopyexamination,IOP measurement by Goldmannapplanation tonometry and dilated fundus examination. Blood analysis for serum hemoglobin, serum iron concentration and the mean corpuscular volume was performed for every subject.

RNFL thickness was obtained with optic disc: 3 D scan protocol 512 × 128 (128 horizontal scan lines comprised of 512 A-scans), 6 × 6 mm by Topcon 3 D OCT- 2000 FA plus. Best scan with image quality factor (IQF) >70 (signal >7) was used for the analysis. Average, inferior, superior, nasal and temporal quadrant RNFL measurements were noted. Right eye values of the subjects were used for statistical analysis.

Statistical analysis were performed using the Statistical Package for Social Sciences 21.0 for Windows (SPSS Inc., Chicago, IL, USA). Correlation analysis was performed with Pearson's correlation coefficient analysis test. Probability valueof 0.05 or less ($p<0.05$) was considered statistically significant.

Results:-

The study included 30 adult female patients who had iron deficiency anemia (hemoglobin <12 g/dl, serum iron <50 µg/dl, mean corpuscular volume <80 fl red cell) (mean age 33.57 ± 7.48 with range 20–47 years), and of 30 healthy control females (mean age 33.77 ± 6.32 with range 22–46) years ($P = 0.87$). The clinical and laboratory data of the anemic patients and control subjects are presented in table 1.There was no statistically significant difference ($p >0.05$) between the patients and controls as regards to the refractive errors, the intraocular pressure (IOP) and cup/disc ratio (C/D ratio). But there was statistically significant difference between the patients and controls as regards to haemoglobinconcentration (P=0.000017), serum iron (P=0.00002) and mean corpuscular volume (p=0.000173).

Table 1:- The clinical and laboratory data (mean ± sd) of female patients with iron deficiency anemia and healthy control females.

	Anemic females	Healthy controls	P value
Age	33.57 ± 7.48	33.77 ± 6.32	0.87
Refractive error	1.09 ± 0.56	0.96 ± 0.62	0.48
Intraocular pressure mm/Hg	13.32 ± 1	13.2 ± 1.1	0.465
Cup/disc ratio	0.29 ± 0.3	0.28 ± 0.02	0.69
Haemoglobin g/dl	8.62 ±0.97	13.03 ± 0.62	0.000017
Serum iron µg/dl	24.5 ± 2.96	86.97 ± 5.32	0.00002
Mean corpuscular volume fl	71.5 ± 2.25	85.9 ± 2.2	0.000173

There was statistically significant difference ($P<0.05$) between the anemic female patients and healthy control females controls as regards to retinal nerve fiber layer(RNFL) measurement by Topcon 3-D OCT 2000.As in table2.

The anemic patients had thinner average, inferior, superior, nasal and temporal RNFL thickness than the healthy control subjects.

The mean RNFL thickness in anemic female patients was 89.5 ± 2.014, and in healthy control females was 94.22 ± 1.486 ($P = 0.000026$). The mean of inferior quadrant RNFL thicknesses of anemic female patients was 118.83 ± 2.75, and in healthy control females was 124.47 ± 1.93 ($P = 0.000032$). The mean of superior quadrant RNFL thicknesses of anemic female patients was 109.83 ± 2.3, and in healthy control females was 114.47 ± 1.7 ($P = 0.00043$). The mean of nasal quadrant RNFL thicknesses of anemic female patients was 69.4 ± 1.81, and in healthy control females was 73.7 ± 1.7 ($P = 0.000028$). The mean of temporal quadrant RNFL thicknesses of anemic female patients was 59.93 ± 1.95, and in healthy control females was 64.3 ± 1.7 ($P = 0.00053$).

Table 2:- Peripapillary retinal nerve fiber layer thicknesses(by SD-OCT) of female patients with iron deficiency anemia and healthy control females.

Peripapillary retinal nerve fiber layer thicknesses	Anemic females	Healthy controls	P value
Average µm	89.5 ± 2.014	94.22 ± 1.486	0.000026
Inferior µm	118.83 ± 2.75	124.47 ± 1.93	0.000032
Superior µm	109.83 ± 2.3	114.47 ± 1.7	0.00043
Nasal µm	69.4 ± 1.81	73.7 ± 1.7	0.000028
Temporal µm	59.93 ± 1.95	64.3 ± 1.7	0.00053

The correlation analysis revealed that, There was positive correlation between mean RNFL thickness and hemoglobin (*r1* = 0.537, p1=0.002) and iron (*r* 2= 0.328, p2=0.005).

Discussion:-

Iron deficiency anemia is the most prevalent type of anemia worldwide.[15]
40–50% of the women in the childbearing age had anemia, which commonly iron deficiency anemia.[16],

It is well known that iron has significant functions in central nervous system, mainly nerve myelination and neurotransmitter synthesis. [17] Iron is essential for myelin synthesis, either directly as a cofactor of lipid cholesterol biosynthesis or indirectly as an oxidative metabolism process in oligodendrocytes. [3], High level of iron in newborns indicates its important role in the development of central nervous system.

The current study found that adult female patients with iron deficiency anemia had significantly ($p<0.05$) thinner average, inferior, superior, nasal and temporal RNFL thickness compared to healthy control subjects. And also there was positive correlation between mean RNFL thickness and both of hemoglobin and iron level.

The study of OncelAcir *et al*. reported that peripapillary RNFL was thinner in the nasal and inferior quadrants in adult female patients with IDA compared to age and sex-matched healthy subjects. While macula ganglion cell-inner plexiform layer (GCL+) measurements revealed similar values in both groups. [18]

The study of Türkyilmaz *et al.*on the children with iron deficiency anemia, found that: the children with IDA have thinner average, superior and inferior RNFLthickness than controls. And there was statistically significant correlation between mean RNFL, upper, lower, and temporal quadrant RNFL thickness and average values of hemoglobin. [19]

Further study by Aksoy *et al*. to evaluate RNFL thickness in children with thalassemia major and children with iron deficiency anemia, detect that RNFL thickness was decreased in inferior quadrant in IDA group and there was positive correlation between RNFL thickness and hemoglobin level. While in thalassemia major group, RNFL was decreased in all four quadrants compared to the control and IDA group. [20]

All finding suggests that IDA may have significant impact on RNFL thickness. The difference between studies may be due to difference in population (age and race), type and severity of anemia or variation of SD-OCT instruments.

The reduction in RNFL thickness in this study may be contributed to both hypomyelination due to iron deficiency and hypoxia. Evidence that suggest the role of iron deficiency, occurrence of neural mediated syncope and restless leg syndrome in iron deficiency. [21] [22] As regards to hypoxia, thinning of RNFL thickness in ischemic retinopthy as vascular occlusion and sickle cell disease and in children with thalassemia. [2] [20]In addition to dopminergic dysfunction may have role in thinning of RNFL in iron deficiency anemia as dopamine is the major retinal neurotransmitter. This is explaining reduction of blinking rate in iron deficiency anemia due to dopminergic dysfunction. [6] [23]Also iron deficiency anemia may be associated with decrease in trace elements (copper and zinc) due to metabolic interaction so reduction of RNFL thickness may be due to deficiency of trace elements besides iron. [24] [25]

The limitations of our study are small sample size, we couldn't classify the patients according to the duration and severity of anemia as we did not know how long the patients had been anemic. It is, however, not possible to know the duration of anemia precisely. We did not evaluate RNFL thickness after treatment of anemia.

Our conclusion is that, iron deficiency anemia leads to thinning of RNFL thickness so it a significant impact on assessment of many ophthmic disorder that affect RNFL thickness like glaucoma and optic neuropathy.Further studies are needed to evaluate the potential effect of treatment on RNFL thickness.

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